d) determining that the agent does not bind to the human mitochondrial membrane protein, thereby identifying the agent with antifungal specificity.

43. (Reiterated.) A method for identifying a specific antiprotozoal agent, the method comprising:

a) combining at least one agent with a protozoal TIM17,

b) identifying an agent which binds to the protozoal TIM17,

c) combining said agent with the human mitochondrial membrane protein of claim 17, and

d) determining that said agent does not bind to the human mitochondrial membrane protein, thereby identifying the agent with antiprotozoal specificity.

REMARKS

Claims 2-10 and 17-43 are pending in the application. Claims 2-10, 19-31, and 34-43 are withdrawn as being drawn to non-elected inventions. Applicants reserve the right to prosecute the non-elected claims in subsequent divisional applications. Applicants thank the Examiner for acknowledging that method claims limited to the scope of the allowable product claims will be rejoined and examined at the time the product claims are indicated as being allowable (Office Action, page 2). Claims 17, 32, and 33 have been amended to clarify the subject of the claimed invention. Support for the additional claim limitations in claims17 is found in the specification at page 46, line 24, through page 47, line 16, where specific assays for human mitochondrial membrane protein (HuTIM17) activity is described, and at page 28, line 3-10, where the specification describes methods to screen antibodies for desired specificities. No new matter is added by these amendments. Entry of these amendments is respectfully requested. Therefore, claims 17, 18, 32, and 33 are currently being examined on the merits. Applicants thank the Examiner for finding that claims 18 and 31 are free of prior art (Office Action, page 12)

Specification

The misspelled word in the specification has been corrected as suggested by the Examiner. Applicants thank the Examiner for pointing out this error.

Rejections under 35 U.S.C. 112, first paragraph

Claims 17, 18, 32, and 33 are rejected under 35 U.S.C. 112, first paragraph as allegedly not enabled by the specification. The Examiner alleged that the specification did not teach how to use a pharmaceutical composition for the treatment of scleroderma, asthma, and cancer. Applicants respectfully traverse.

Claims 32 and 33 recite a pharmaceutical composition comprising an effective amount of the claimed polypeptides. The Examiner is reminded that both claims 32 and 33 are composition claims, and not method of use claims. As such, Applicants have provided extensive teachings regarding how to make and use the pharmaceutical compositions as claimed in claims 32 and 33. There are over 4 pages in the specification devoted solely to teach one with ordinary skill in the art how to make and use the pharmaceutical composition, as disclosed from page 30 to page 34. The parameters taught there include various means of administering the pharmaceutical composition, active ingredients, passive ingredients, dosages, coatings, formulations, preparations of the pharmaceutical composition, etc. Having obtained the claimed polypeptides in the instant invention, the skilled artisan would be able to make and use pharmaceutical compositions comprising such polypeptides following the teachings discussed above. Thus, no undue experimentation is needed by the ordinary skilled artisan in order to practice the invention as claimed in claims 32 and 33.

The common phrase "an effective amount" may or may not be indefinite. The proper test is whether or not one skilled in the art could determine specific values for the amount based on the disclosure. See In re Mattison, 509 F.2d 563, 184 USPQ 484 (CCPA 1975). The phrase "an effective amount...for growth stimulation" was held to be definite where the amount was not critical and those skilled in the art would be able to determine from the written disclosure, including the examples, what an effective amount is. In re Halleck, 422 F.2d 911, 164 USPQ 647 (CCPA 1970). The phrase "an effective amount" has been held to be indefinite when the claim fails to state the function which is to be achieved and more than one effect can be implied from the specification or the relevant art. In re Fredericksen 213 F.2d 547, 102 USPQ 35 (CCPA

1954). The more recent cases, however, have tended to accept a limitation such as "an effective amount" as being definite when read in light of the supporting disclosure and in the absence of any prior art which would give rise to uncertainty about the scope of the claim. In Ex parte Skuballa, 12 USPQ2d 1570 (Bd. Pat. App. & Inter. 1989), the Board held that a pharmaceutical composition claim which recited "an effective amount of a compound of claim 1" without stating the function to be achieved was definite, particularly when read in light of the supporting disclosure which provided guidelines as to the intended utilities and how the uses could be effected.

In this case, the specification provides sufficient teachings on the meaning of the term "an effective amount", and on how to determine the effective amount of the claimed polypeptide in the pharmaceutical composition. For example, on page 33, lines 4-7, Applicants teach that the pharmaceutical compositions suitable for use in the invention include compositions wherein the active ingredients are contained in an effective amount to achieve the intended purpose. The determination of an effective dose is well within the capability of those skilled in the art. Furthermore, Applicants teach that an effective amount of the active ingredient, i.e. the claimed polypeptide, refers to the amount of the polypeptide which ameliorates the symptoms or conditions, which is the intended therapeutic efficacy. See page 33, lines 13-15. Such therapeutic efficacy may be determined by the standard pharmaceutical procedures in cell cultures and experimental animals (page 33, lines 15-18). Thus, it is clear to one with ordinary skill in the art what the term "effective amount" means in the context of the invention, in light of the teachings in the specification, and the general knowledge in the relevant art. No undue experimentation is necessary to determine the effective amount of the polypeptide in order to carry out the claimed invention in claims 32 and 33. The Examiner is respectfully requested to withdraw this rejection.

However, in the interest of expediting the prosecution of the instant application, Applicants have amended claims 32 and 33 to delete the recitation of "pharmaceutical" in the term "pharmaceutical composition", as suggested by the Examiner in the office action (page 5). Therefore, the Examiner is respectfully requested to withdraw the rejections of claims 32 and 33 under 35 U.S.C. 112, first paragraph.

Claims 17 and 18 are rejected under 35 U.S.C. 112, first paragraph, as allegedly

containing matter not described in the specification in such a way as to reasonably convey to one of skill in the art that the inventors had possession of the claimed invention. The rejection is directed towards fragments of SEQ ID NO:1 as claimed in 17 (c)and (d). The Examiner alleges these fragments would not function as would the full-length protein encoded by SEQ ID NO:1, and that the claims therefore encompass "a variety of subgenera with widely varying attributes", which are not sufficiently well described.

Applicants point out in response that claim 17 in fact specifically encompasses two well-defined categories of fragments. The first such category as recited in claim 17 (c) is biologically active fragments, which are precisely those fragments which retain at least one structural, regulatory, or biochemical functions of the naturally occurring molecule (see the specification at page 6, lines 21-22). To further clarify this claim, it has been amended to recite a biologically-active fragment of the amino acid sequence of SEQ ID NO:1, wherein said biologically-active fragment has HuMIM17 activity. The biological activity of such a fragment may be measured using the assays described in the specification at page 46, line 24, through page 47, line 16. Claim 17 (d) has also been amended for clarity to recite an immunologically active fragment of the amino acid sequence of SEQ ID NO:1, wherein said immunologically active fragment generates an antibody that specifically binds to the polypeptide encoded by SEQ ID NO:1. The term "immunologically-active", which replaces the previously used term "immunogenic", is clearly defined on page 6, lines 22-25. Methods to screen antibodies for desired specificities are described in the specification at page 28, lines 3-10. Thus one of skill in the art would reasonably understand the subject matter encompassed by the claims and that Applicants were in possession of the claimed invention at the time of filing. Withdrawal of the rejections of claim 17 and dependent claim 18 under 35 U.S.C. 112, first paragraph, is therefore respectfully requested.

Rejection under 35 U.S.C. 112, second paragraph

Claims 17, 18, 32, and 33 are rejected under 35 U.S.C. 112, second paragraph as being indefinite. The Examiner alleged that the terms "naturally-occurring", "biologically-active" and "immunogenic" in claim 17, as well as the phrase "effective amount" in claim 32, are not clear. Applicants respectfully traverse.

It is well settled in patent law that "[t]he test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification." *Miles Lab, Inc. v. Shandon Inc.*, 27 USPQ2d 1123, 1126 (Fed. Cir. 1993), citing *Orthokinetics Inc. v. Safety Travel, Chairs, Inc.*, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986). In the instant case, Applicants assert that claim 17 as amended has clearly defined terms and is fully supported by the teachings in the specification. One with ordinary skill in the art would readily understand the metes and bounds of the claim in light of the specification. For instance, the term "naturally-occurring" is commonly used in the art to designate a protein, polypeptide, or other molecules which are found in nature. It is understood in the art that naturally-occurring proteins are distinguished from those that are synthetic, or otherwise made by man. The term "biologically-active" is clearly defined in the definition section of the specification on page 6, lines 21-22, as referring to a protein having structural, regulatory, or biochemical functions of a naturally occurring molecule. The term "immunologically-active", which replaces the previously used term "immunogenic", is clearly defined on page 6, lines 22-25, as referring to the capability of the natural, recombinant, or synthetic protein to induce a specific immune response and to bind with specific antibodies. Furthermore, Claim 17 has been amended to further clarify the intended meaning of "biologically-active" and "immunologically-active," as discussed above. The term "effective amount" is also clearly defined in the specification as discussed above. Thus, independent claim 17, and the dependent claims 18, 32, and 33, are not indefinite because the objected terms are clearly defined in the specification, and well understood by one with ordinary skill in the art. Therefore, withdrawal of the rejections of claims 17, 18, 32, and 33 under 35 U.S.C. 112, second paragraph is respectfully requested.

Rejection under 35 U.S.C. 101/112, first paragraph for lack of utility

Claims 17 and 18 are rejected under 35 U.S.C. 101 as lacking either a specific asserted utility or a well established utility. Claims 17, 18, 32, and 33 are also rejected under 35 U.S.C. 112, first paragraph. The Examiner claims that "the specification provides no functional characterization of the polypeptide, no specific tissue distribution of the polypeptide, and no specific disease state in which (sic) these proteins affect." The Examiner further contends that since "there is no information that links expression of the claimed polypeptide to **any specific**

tissue or disorder. Thus, the asserted utility of the claimed nucleic acids is not substantial, specific, or credible." Applicants respectfully submit that both bases for rejection are improper, and in any case, there is a well-established utility for all expressed sequences that has not been considered.

The invention at issue is a polypeptide sequence termed HuTIM17, the sequence of which is disclosed in SEQ ID NO:1. HuTIM17 shares extensive amino acid identity with human preprotein translocase and with yeast mitochondrial inner membrane protein 17. Furthermore, as disclosed in the specification on page 12, lines 17-20, Northern analysis shows the expression of HuTIM17 in libraries prepared from a wide variety of cells and tissues, including brain, prostate, melanocytes, pancreas, bladder, lymph node, leukocytes, liver, colon, thyroid, kidney, synovium, heart, lung, and breast. As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which require detailed knowledge of how the polypeptide coded for by the polynucleotide works. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

Any of these uses meets the utility requirements of 35 U.S.C. § 101 and, derivatively, § 112, first paragraph. Under these sections of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); Fuller v. Berger, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999). In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991) the United States Court of Appeal for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is

not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464; *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case the Patent Office bears the burden to demonstrate that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Ids.* To do so, the PTO must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

The rejection fails to demonstrate either that the Applicants' assertions of utility are legally insufficient or that a person of ordinary skill in the art would reasonably doubt that they could be achieved. For these reasons alone the rejections should be withdrawn.

There is, however, an additional, independent reason to withdraw the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999) and Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law. These inconsistencies are discussed separately below.

A. Use of the claimed polypeptides for diagnosis of conditions and disorders characterized by expression of HuTIM17, for toxicology testing, and for drug discovery are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There is a "well-established" use for the claimed invention, there

are specific practical and beneficial uses for the invention, and those uses are substantial. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

1. The use of polynucleotides coding for proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease, as well as the polypeptides themselves, is now "well-established"

In recent years, scientists have developed important techniques for toxicology testing, drug development, and disease diagnosis. Many of these techniques rely on expression profiling, in which the expression of numerous genes is compared in two or more samples. Genes or gene fragments known to be expressed, such as the invention at issue, are tools essential to any technology that uses expression profiling. Likewise, proteome expression profiling techniques have been developed in which the expression of numerous polypeptides is compared in two or more samples. The amino acid sequences of expressed polypeptides or polypeptide fragments are tools essential to any technology that uses proteome expression profiling. See, *e.g.*, Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467 (2000).

The technologies made possible by expression profiling and the DNA and polypeptide tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. One of these techniques is toxicology testing, used in both drug development and safety assessment. Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett, et. al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29(7), 655-691 (1999):

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs.

To the same effect are several other scientific publications, including Emile F. Nuwaysir, et. al., Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Carcinogenesis 24:153-159 (1999); Sandra Steiner and N. Leigh Anderson, *supra*.

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

> ... for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip.

See also Table 1 of Nuwaysir et al. (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray).

The more genes that are available for use in toxicology testing, the more powerful the technique. "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, Environ. Health Perspec. 107(8) 681-685 (1999). Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator, Dr. Cynthia Afshari to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

There are numerous additional uses for the information made possible by expression profiling. Expression profiling is used to identify drug targets and characterize disease. See Rockett et al., *supra.* It also is used in tissue profiling, developmental biology, disease staging, etc. There is simply no doubt that the sequences of expressed human genes all have practical, substantial and credible real-world utilities, at the very least for expression profiling.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter

gene, and chromosomal mapping location, to identify the key gene associated with Tangier disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the rejection failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be withdrawn regardless of their merit.

2. The use of HuTIM17 for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

Even if, *arguendo*, toxicology testing, drug development and disease diagnosis (through expression profiling) are not well-established utilities (which expressly is not conceded), the claimed invention nonetheless has specific utility by virtue of its use in each of these techniques. There is no dispute that the claimed invention is in fact a useful tool in each of these techniques. That is sufficient to establish utility for both the polypeptide and the polynucleotides encoding it.

Nevertheless, the claimed invention is rejected on the grounds that it does not have a "specific utility" absent a detailed description of the actual function of the protein expressed by the claimed nucleic acid or identification of a "specific" disease it can be used to treat. Apparently relying on the Training Materials, the rejection is made based on a scientifically incorrect and legally unsupportable assertion that identification of the family or families of proteins for which the claimed invention codes, without more, does not satisfy the utility

requirement. None of these grounds is consistent with the law.

a. A patent applicant can specify a utility without any knowledge as to how or why the invention has that utility

It is settled law that how or why any invention works is irrelevant to determining utility under 35 U.S.C. § 101: "[I]t is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." *In re Cortright*, 165 F.3d, at 1359 (quoting *Newman v. Quigg*, 877 F.2d 1575, 1581, 11 USPQ2d 1340 (Fed. Cir. 1989)). *See also Fromson v. Advance Offset Plate, Inc.*, 720 F.2d 1565, 1570, 219 USPQ 1137 (Fed. Cir. 1983) ("[I]t is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests."). It follows that the patent applicant need not set forth the particular functionality of the claimed invention to satisfy the utility requirement.

Practical, beneficial use, not functionality, is at the core of the utility requirement. *Supra* (introduction to § I). So long as the practical benefits are apparent from the invention without speculation, the requirement is satisfied. *Standard Oil* Co. v. *Montedison*, 664 F.2d 356, 374, 212 USPQ 327 (3d Cir. 1981); *see also Brana*, 51 F.3d at 1565. To state that a biological molecule might be useful to treat some unspecified disease is not, therefore a specific utility. *In re Kirk*, 376 F.2d 936, 945, 153 USPQ 48 (C.C.P.A. 1967). The molecule might be effective, and it might not.

However, unlike the synthetic molecules of *Kirk*, the claimed invention is **known** to be useful. It is not just a random sequence of speculative use. Because it is expressed in humans, a person of ordinary skill in the art would know how to use the claimed sequence -- without any guesswork -- in toxicology testing, drug development, and disease diagnosis regardless of how the polynucleotide or the protein it encodes actually functions. The claimed invention could be used, for example, in a toxicology test to determine whether a drug or toxin causes any change in the expression of HuTIM17. Similarly, the claimed invention could be used to determine whether a specific medical condition, such as cancer, affects the expression of HuTIM17 and, perhaps in conjunction with other information, serve as a marker for a particular disease or condition.

In fact, the claimed invention could be used in toxicology testing and diagnosis without **any** knowledge (although this is not the case here) of the protein for which it codes: it could

serve, for example, as a gene expression control in toxicology testing. Diagnosis of disease (or fingerprinting using expression profiles) can be achieved using arrays of numerous identifiable, expressed DNA sequences, or by two-dimensional gel analysis of the expressed proteins themselves, notwithstanding lack of any knowledge of the proteins they encode.

b. A patent applicant may specify a utility that applies to a broad class of inventions

The fact that the claimed invention is a member of a broad class (such as DNA sequences or the proteins they encode expressed in humans) that includes sequences other than those claimed that also have utilities in toxicology testing, drug discovery, disease diagnosis, etc. does not negate utility. Practical utilities can be directed to classes of inventions, irrespective of function, so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. *Montedison*, 664 F.2d at 374-75. The law has long assumed that inventions that achieve a practical use also achieved by other inventions satisfy the utility requirement. For example, many materials conduct electricity. Likewise, many different plastics can be used to form useful films. *Montedison*, 664 F.2d at 374-75; *Natta*, 480 F.2d at 1397. This is a general utility (practical films) that applies to a broad class of inventions (plastics) which satisfies the utility requirement of 35 U.S.C. § 101.

Not all broad classes of inventions are, by themselves, sufficient to inform a person of ordinary skill in the art of the practical utility for a member of the class. Some classes may indeed convey too little information to a person of ordinary skill in the art. These may include classes of inventions that include both useful and nonuseful members. *See In re Ziegler*, 992 F.2d 1197, 1201, 26 USPQ2d 1600 (Fed. Cir. 1993). In some of these cases, further experimentation would be required to determine whether or not a member of the class actually has a practical use. *Brenner*, 383 U.S. at 534-35.

The broad class of steroids identified in *Kirk* is just such a class. It includes natural steroids (concededly useful) and man-made steroids, some of which are useful and some of which are not. Indeed, only a small fraction of the members of this broad class of invention may be useful. Without additional information or further experimentation, a person of ordinary skill in the art would not know whether a member of the class falls into the useful category or not. This could also be the case for the broad class of "plastic-like" polypropylenes in *Ziegler*, which

includes many -- perhaps predominately -- useless members.

The PTO routinely issues patents whose utility is based solely on the claimed inventions' membership in a class of useful things. The PTO presumably would issue a patent on a novel and nonobvious fishing rod notwithstanding the lack of any disclosure of the particular fish it might be used to catch. The standard being promulgated in the Guidelines and in particular as exemplified in the Training Materials, and being applied in the present rejection, would appear to warrant a rejection, however, on the grounds that the use of the fishing rod is applicable to the general class of devices used to catch fish.

The PTO must apply the same standard to the biotechnological arts that it applies to fields such as plastics and fishing equipment. *In re Gazave*, 379 F.2d 973, 977-78, 154 USPQ 92 (CCPA 1967) *quoting In re Chilowsky*, 299 F.2d 457, 461, 108 USPQ 321 (CCPA 1956) ("[T]he same principles should apply in determining operativeness and sufficiency of disclosure in applications relating to nuclear fission art as in other cases."); *see also In re Alappat*, 33 F.3d 1526, 1566, 31 USPQ2d 1545 (Fed. Cir. 1994) (Archer, C.J., concurring in part and dissenting in part) ("Discoveries and inventions in the field of digital electronics are analyzed according to the aforementioned principles [concerning patentable subject matter] as any other subject matter."). Indeed, there are numerous classes of inventions in the biotechnological arts that satisfy the utility requirement.

Take, for example, the class of interleukins expressed in human cells of the immune system. Unlike the classes of steroids or plastic-like polypropylenes in *Kirk* and *Ziegler*, all of the members of this class have practical uses well beyond "throwaway" uses. All of them cause some physiological response (in cells of the immune system). All of the genes encoding them can be used for toxicology testing to generate information useful in activities such as drug development, even in cases where little is known as to how a particular interleukin works. No additional experimentation would be required, therefore, to determine whether an interleukin has a practical use. It is well-known to persons of ordinary skill in the art that there is no such thing as a useless interleukin.

Because all of the interleukins, as a class, convey practical benefit (much like the class of DNA ligases identified in the Training Materials), there is no need to provide additional information about them. A person of ordinary skill in the art need not guess whether any given inter-

leukin conveys a practical benefit or how that particular interleukin works.

Another example of a class that by itself conveys practical benefits is the G protein-coupled receptors ("GPCRs"). GPCRs are well-known as intracellular signaling mediators with diverse functions critical to complex organisms. They perform these functions by binding to and interacting with specific ligands. They are targets of many current drug treatments, including anti-depressants, anti-histamines, blood pressure regulators, and opiates.

Newly-identified GPCRs are used intensively in the real-world, even in cases where neither the specific ligand that binds to the GPCR or the precise biological function of the GPCR is known. Newly identified GPCRs are used, for example, as toxicity controls for drug candidates known to bind other GPCRs. Because a person of ordinary skill in the art would know how to use any GPCR to achieve a practical benefit, even without any detailed or particular knowledge as to how it works, GPCRs as a class meet the utility requirement.

In fact, **all** isolated and purified naturally-occurring polynucleotide sequences which are expressible (i.e., which are not pseudogenes that are never expressed during any natural biological process) can be and **are** used in a real-world context as tools for toxicological testing, e.g., for drug discovery purposes. This utility applies to all sequences actually expressed, yet in each case, the utility of the sequence is quite specific, e.g., insofar as it is used to detect its own specific complementary sequence in a sample containing many different sequences.

Human mitochondrial membrane proteins, like interleukins, GPCRs and fishing rods is a class that by itself conveys practical benefits. Unlike steroids and "plastic-like" polypropylenes, all of the mitochondrial membrane proteins are expressed by humans, and all of them can be used tools for toxicology testing. The claimed invention could be used, for example to determine whether a drug candidate affects the expression of mitochondrial membrane proteins in humans, how it does so, and to what extent. Just as there are no useless interleukins and GPCRs, there are no useless mitochondrial membrane proteins. As these are practical, real-world uses, the application need not describe particular functionality or medical applications that would only supplement the utilities known to exist already.

3. Because the use of HuTIM17 in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself, the claimed invention has substantial utility.

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

The claimed invention's use as a tool for toxicology testing is just such a practical, real-world use. The PTO nonetheless rejected the claims at issue on the ground that the use of an invention as tool for research is not a "substantial" use. Because the PTO's rejection assumes a substantial overstatement of the law, it must be withdrawn.

There is no authority for the proposition that use as a tool for research is not a substantial utility. In fact, the PTO issues patents for inventions whose only use is to facilitate research, such as DNA ligases. These are acknowledged by the PTO's Training Materials themselves to be useful.

Only a limited subset of research uses are not "substantial" utilities: those in which the only known use for the claimed invention is to be an **object** of further study, thus merely inviting further research. This follows from *Brenner*, in which the U.S. Supreme Court held that a process for making a compound does not confer a substantial benefit where the only known use of the compound was to be the object of further research to determine its use. *Id.* at 535. Similarly, in *Kirk*, the CCPA held that compound would not confer substantial benefit on the public merely because it might be used to synthesize some other, unknown compound that would confer substantial benefit. *Kirk*, 376 F.2d at 940, 945 ("What Applicants are really saying to those in the art is take these steroids, experiment, and find what use they do have as medicines."). Nowhere do those cases state or imply, however, that a material cannot be patentable if has some other beneficial use in research.

As used in toxicology testing, drug discovery, and disease diagnosis, the claimed invention has a beneficial use in research other than studying the claimed invention. It is a tool, rather than an object, of research. The claimed invention has numerous other uses as a research tool, each of which alone is a "substantial utility". These include use of the claimed polypeptide sequences in disease diagnosis, expression profiling, and drug discovery (Specification, page 24, lines 27-30, through page 24, lines 1-27; page 35, lines 29-30, through page 36, lines 1-7; page 38, lines 26-30, through page 39, lines 1-11.)

4. Objective evidence corroborates the utilities of the claimed invention

There is in fact no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. Indeed, "real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all expressed genes, in particular genes having medical and pharmaceutical significance such as the instant sequence. (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Applicants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the claimed sequence and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

B. The Patent Examiner Failed to Demonstrate That a Person of Ordinary Skill in the Art Would Reasonably Doubt the Utility of the Claimed Invention

In addition to alleging a "specific" use for the claimed subject matter, a patent applicant must present proof that the claimed subject matter is in fact useful. *Brana*, 51 F.3d at 1565-66. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

The amount of evidence required to prove utility depends on the facts of each particular case. *In re Jolles*, 628 F.2d 1322, 1326, 206 USPQ 885 (CCPA 1980). "The character and amount of evidence may vary, depending on whether the alleged utility appears to accord with or to contravene established scientific principles and beliefs." *Id.* Unless there is proof of "total incapacity," or there is a "complete absence of data" to support the applicant's assertion of utility, the utility requirement is met. *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571, 24 USPQ2d 1401 (Fed. Cir. 1992); *Envirotech*, 730 F.2d at 762.

A patent applicant's assertion of utility in the disclosure is presumed to be true and

correct. *In re Cortright*, 165 F.3d at 1356; *Brana*, 51 F.3d at 1566. If such an assertion is made, the Patent Office bears the burden in the first instance to demonstrate that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved. *Ids.* To do so, the PTO must provide evidence or sound scientific reasoning. *See Langer*, 503 F.2d at 1391-92. If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The Revised Guidelines are in agreement with this procedure. *See* Revised Interim Guidelines at ¶ ¶ 3-4.

The issue of proof often arises in the chemical and biotechnological arts when the patentee asserts a utility for a claimed chemical compound based on its homology or similarity to another compound having a known, established utility. In such cases, the applicant can demonstrate "substantial likelihood" of utility by demonstrating a "reasonable correlation" between the utility -- not the function -- of the known compound and the compound being claimed. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1565, 39 USPQ2d 1895 (Fed. Cir. 1996). Accordingly, under *Brana*, the Patent Office must accept the asserted utility unless it can show that a person of ordinary skill in the art would reasonably doubt that a "reasonable correlation" exists. If the Patent Office makes such a showing, however, the applicant may submit evidence in support of the correlation.

In the present case, the specification (page 12, lines 10-20) clearly discloses that the claimed HuTIM17 has

> . . . chemical and structural homology with human preprotein translocase (GI 1770564; SEQ ID NO:3) and yMIM17 (GI 557267; SEQ ID NO:4). In particular, HuTIM17 and human preprotein translocase share 75% amino acid sequence identity; HuTIM17 and yMIM17 share 48% amino acid sequence identity (Fig. 2). As illustrated by Figs. 3 and 4, HuTIM17 and yMIM17 have similar hydrophobicity plots. HuTIM17 has potential transmembrane domains comprising amino acids 16 to 34, 63 to 82, and 94-135 of SEQ ID NO:1; the latter domain is of sufficient length to span the membrane twice.

Thus the only evidence of record shows that a person of ordinary skill in the art would not doubt that HuTIM17 is in fact a human mitochondrial membrane protein, which is known to have a specific utility in the study of mitochondrial import processes.

By ignoring the "reasonable correlation" requirement in the case law and failing to

illustrate the procedure established by *Brana*, the Examiner has failed to set forth a proper *prima facie* case, and the rejection does not shift the burden of proof to Applicants for rebuttal. In fact, the rejection must be withdrawn, as the Examiner has failed to meet PTO's burden in the first place of establishing a proper rejection. There is no proper rejection for Applicants to rebut.

C. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities which meet the statutory requirements, and "general" utilities which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at p.52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000)("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.")).

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus incredible, "throw-away" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food" do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Applicants are not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. *See Brana, supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § II.B.2 (*Montedison,* 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions heretofore considered to be patentable, and that have indisputably benefitted the public, including the claimed invention. *See supra* § II.B. Thus the Training Materials cannot be applied consistently with the law.

D. To the extent the rejection of the patented invention under 35 U.S.C. § 112, first paragraph, is based on the improper rejection for lack of utility under 35 U.S.C. § 101, it must be withdrawn

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112., first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

Rejection under 35 U.S.C. 102

Claim 17 is rejected under 35 U.S.C. 102 as being anticipated by various references including Accession Numbers P39515, Q02310, Maarse et al., Ryan et al., and U.S. Patent #5,876,991. The Examiner alleged that the cited references disclose a polypeptide comprising an amino acid sequence that is a biologically active fragment and an immunogenic fragment of the amino acid sequence of SEQ ID NO:1. Applicants respectfully traverse.

It is well established in patent law that a reference is anticipatory only if all elements of the claimed invention are disclosed in the reference. *In re Paulsen*, 31 USPQ2d 1671, 1673 (Fed. Cir. 1994). In the instant case, claim 17 as amended herein recites a biologically-active fragment of the amino acid sequence of SEQ ID NO:1 wherein said biologically-active fragment has HuMIM17 activity, and an immunologically-active fragment of the amino acid sequence of SEQ ID NO:1, wherein said fragment is capable of generating an antibody that specifically binds to the polypeptide depicted in SEQ ID NO:1. These limitations are not found anywhere in the cited references. Thus, the rejection of claims 17 under 35 U.S.C. 102 is improper, and the Examiner is respectfully requested to withdraw such rejection.

Rejection under 35 U.S.C. 103

Claim 32 is rejected under 35 U.S.C. 103(a) as being unpatentable over Accession Numbers P39515, Q02310, Maarse et al., Ryan et al., and U.S. Patent #5,876,991, in view of Harlow and Lane. The Examiner alleged that Harlow and Lane provided that motivation to formulate a pharmaceutical composition using the polypeptide taught in the above references, thus rendering the instant invention obvious. Applicants respectfully traverse.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the reference itself or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. Second, there must

be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations. The teachings or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on the applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicants assert that the Patent Office has not established a *primae facie* case of obviousness in the instant case. Specifically, the cited references do not teach or suggest all the claim limitations. As discussed above, Accession Numbers P39515, Q02310, Maarse et al., Ryan et al., and U.S. Patent #5,876,991 do not teach a biologically active fragment of the amino acid sequence of SEQ ID NO:1 wherein said biologically-active fragment has HuMIM17 activity, or an immunologically-active fragment of the amino acid sequence of SEQ ID NO:1, wherein said fragment is capable of generating an antibody that specifically binds to the polypeptide depicted in SEQ ID NO:1. Such limitations are also nowhere to be found in Harlow and Lane, which is a textbook on generalized protocols in immunology. Thus, the Examiner is respectfully requested to withdraw the rejection of claim 32 under 35 U.S.C. 103.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Attorney at (650)855-0555.

Pursuant to the attached Petition For Extension of Time, the Commissioner is hereby authorized to charge the fee of **$110.00**, or any additional fee that may be required, or credit any overpayment to Incyte Pharmaceutical, Inc. Deposit Account No. **09-0108.**

This form is enclosed in duplicate.

Respectfully submitted,

INCYTE GENOMICS, INC.

Date: 9/25/00

Peng Ben Wang, J.D.
Reg. No. 41,420
Direct Dial Telephone: (650) 621 -7574

Date: September 25, 2000

Barrie D. Greene
Reg. No. 46,740
Direct Dial Telephone: (650) 621-7576

3160 Porter Drive
Palo Alto, California 94304
Phone: (650) 855-0555
Fax: (650) 849-8886